DEPARTMENT OF HEALTH & HUMAN SERVICES

667 HFI-35 7/31/97

Public Health Service

FOOD & DRUG ADMINISTRATION
466 FERNANDEZ JUNCOS AVENUE
SAN JUAN, P.R. 00901-3223

June 27, 1997

WARNING LETTER
SJN-97-18

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. Robert Bosclair
Sr. VP Merck Manufacturing Division
Merck & Co., Inc.
P.O. Box 100
Whitehouse Station, NJ 08889-0100

Dear Mr. Bosclair:

During an inspection of your veterinary drug manufacturing facility, Merck Sharp & Dohme Quimica P.R., located at Rd. #2, Km. 56.7, Cruce Davila, Barceloneta, PR conducted from March 20 to May 13, 1997, our investigators found significant deviations from the Good Manufacturing Practice Regulations for Finished Pharmaceuticals (Title 21, Code of Federal Regulations, Part 211) in conjunction with your firm's manufacture of injectable and oral veterinary drugs causing these products to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act, as follows:

1. Failure to maintain adequate controls in the Water for Injection System for Factory 4 in that samples from the compressed clean steam and reverse osmosis systems are frequently out-of-specifications for microorganisms, specifically Burkholderia (Pseudomonas) cepacia. You have failed to identify the source of this contamination or to take sufficient corrective actions to prevent reoccurrence of the positive findings. The Water for Injection from this system is used to clean equipment and stoppers for sterile injectable products and to formulate oral products. Use of water contaminated with microorganisms for these purposes is in violation of 21 CFR 211.42 (c)(10)(v), 211.84 (d)(6) and 211.94 (c).

Although not listed on the FD-483, you should be advised that review of your supplier's guarantee for the reference standard you are using for LAL testing shows it is guaranteed only "as a mean for a range of lysates". This reference standard needs to be standardized against a U.S.P. reference standard in accordance with U.S.P. XXIII <85> **BACTERIAL ENDOTOXINS TEST, REFERENCE STANDARD AND CONTROL STANDARD ENDOTOXINS.**

We acknowledge receipt of your letter, dated June 10, 1997. Your responses to FD-483 observation 1 was not adequate for the reasons mentioned under item 1 above. The responses to the other FD-483 observations appear, if fully implemented, to adequately address the other concerns of the investigators.

The above identification of violations is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to assure adherence with each requirement of the Good Manufacturing Practice Regulations. Federal agencies are advised of the issuance of all warning letters about drugs so that they may take this information into account when considering the award of contracts.

Please notify the San Juan District office in writing within 15 working days of receipt of this letter, of the specific steps you have taken to correct the noted violations, including an explanation of each step being taken to prevent the recurrence of these or similar violations.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. These include seizure and/or injunction.

Your reply should be sent to the Food and Drug Administration, San Juan District Office, 466 Fernandez Juncos Ave., San Juan, Puerto Rico 00906-3223, Attention: Mary L. Mason, Compliance Officer.

Sincerely,

Samuel Jones
District Director